HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

Test Plan
For
Primene™ 81-R Amine
CAS Number 68955-53-3

PREPARED BY:

ROHM AND HAAS COMPANY

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OVERVIEW

The Rohm and Haas Company hereby submits for review and public comment the test plan for Primene™ 81-R Amine (CAS No.: 68955-53-3) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data on Primene™ 81-R Amine in conjunction with EPA-acceptable predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that in total these data are adequate to fulfill all the requirements of the HPV program without need for the conduct of any new or additional tests.

Primene™ 81-R Amine is a primary aliphatic amine with highly branched alkyl chains ($C_{12} - C_{14}$) in which the amino nitrogen atom is linked to a tertiary carbon. This material has unique chemical and physical properties, including unusually good resistance to oxidation, fluid character and low viscosity over a wide range of temperature, outstanding color stability, and high solubility in petroleum hydrocarbons. Primene™ 81-R Amine is used as a chemical intermediate in a wide range of applications. These include the use of Primene™ 81-R Amine in the formulation of solvent base dyes subsequently used to color aluminum foils, as a lubricant or surfactant in metal working fluids, and as an anti-corrosive agent. In addition, Primene™ 81-R Amine is added to crude oil on a ppm-basis proportional to the amount of mercaptans found in the unrefined oil.

In conclusion, an adequate assessment and summarization of all the SIDS endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests.

TEST PLAN SUMMARY

CAS No. 68955-53-3	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL –CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Density	Y	-	-	-	Y	Y	N
Vapor Pressure	Y	-	-	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
Surface Tension	Y	-	Y	-	N	Y	N
Flash Point	Y	-	Y	-	N	Y	N
Auto Flammability	Y	-	Y	-	N	Y	N
Explosive Properties	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y[1]	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y	-	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
Chronic Toxicity to Fish	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	Y	-	-	Y	Y	N
Repeated Dose Toxicity	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was determined from analyses that followed the American Society for Testing and Materials (ASTM) Test Method D-97. No data on whether test was conducted in compliance with Good Laboratory Practice (GLP), but test was conducted by recognized scientific standards.

Boiling Point - A value for this endpoint was determined from analyses that followed ASTM Test Method D-1078. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Density - A value for this endpoint was determined using an Anton-Parr DMA-46 Densitometer at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Vapor Pressure - A value for this endpoint was determined from analyses that followed ASTM Test Method D-2879. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards. A value for this endpoint also was derived from measured saturated vapor concentrations during the conduct of an acute vapor inhalation LC50 study in rats. The saturated vapor concentration was determined using the same sampling and analytical methodology used to measure vapor concentration during the inhalation exposure. The quality of the acute vapor inhalation study in rats was deemed as "reliable without restrictions."

Partition Coefficient - A value for this endpoint was determined from analyses that followed 40CFR Part 792. This test was performed in accordance with GLP regulations.

Water Solubility - A value for this endpoint was determined by capillary gas chromatography at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Surface Tension - A value for this endpoint was measured on the Fisher Surface Tensiometer, Model 20 at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Flash Point - A value for this endpoint was determined by the Pensky Martens Closed Cup method at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Auto Flammability - A value for this endpoint was determined from analyses that followed ASTM Test Method E-659. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Explosive - Properties A value for this endpoint was determined from analyses that followed ASTM Test Method E681-85. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Conclusion: **All physicochemical endpoints have been satisfied with data from well-conducted studies using acceptable methodologies. While no data on whether these tests were conducted in compliance with GLP, the results are of sufficient quality to conclude that no additional testing is needed.**

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using a computer estimation model in EPI suite. The model was unable to estimate atmospheric ozone reaction rates.

Stability in Water - The hydrolytic stability of the C12-C14 Primene™ 81-R Tertiary Alkyl Primary Amines has not been specifically measured in a OECD 111 guideline study. However, based on our understanding of these tertiary alkyl primary amines, we believe that further testing for hydrolytic stability as specified in OECD 111 is not necessary. Under laboratory conditions, Primene™ 81-R Tertiary Alkyl Primary Amines has been shown to be stable under a variety of pH, temperature and storage conditions. In general, the alkanes of which Primene™ 81-R is representative, are typically resistant to hydrolytic degradation (Lyman *et al*., 1982). The Rohm and Haas Company has also attempted to estimate the hydrolysis rates for the C12 and C14 Primene™ 81-R Tertiary Alkyl Primary Amines using Quantitative Structure Activity Relationship (QSAR) modeling using the USEPA EPIWIN Suite version 3.11 (Meylan and Howard, 1999a). The prediction methodology for estimating hydrolysis rates, HYDROWIN, was unable to estimate the hydrolysis rate for C12 and C14 Primene™ 81-R Tertiary Alkyl Primary Amines, suggesting their stability.

Biodegradation- This endpoint is filled by data from a study that followed OECD test guideline 301D and was conducted under GLP assurances. The quality of this study was deemed as "reliable without restrictions."

Fugacity - A value for this endpoint was obtained using the Mackay Level III steady state fugacity model.

Conclusion: **All environmental fate endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total, they are of sufficient quality to conclude that no additional testing is needed.**

C. Ecotoxicity Data

Acute Toxicity To Fish - This endpoint is filled by data from a study that followed OECD test guideline 203 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from a study that followed OECD test guideline 202 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Toxicity to Aquatic Plants - This endpoint is filled by data from a study that followed OECD test guideline 201 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Chronic Toxicity to Fish - This endpoint is filled by data from a study that followed OECD test guideline 210 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Conclusion: **All ecotoxicity endpoints have been satisfied with data from well-conducted studies that followed standardized OECD test guidelines and GLP regulations. The quality of these studies are deemed as "reliable without restrictions" and are therefore of sufficient quality to conclude that no additional testing is needed.**

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from studies assessing toxicity following single oral, dermal, and inhalation exposures. Acute oral toxicity was evaluated in rats and mice, while dermal and inhalation studies used only rats. In addition, studies were conducted in rabbits to assess skin and eye irritation and in guinea pigs for sensitization potential to the skin. These studies followed OECD test guidelines and were conducted under GLP regulations. The quality of these studies were deemed as "reliable without restrictions."

Repeat Dose Toxicity - This endpoint is filled by data from a 28-day dermal exposure study in rats and a 28-day inhalation exposure study in rats. These studies followed OECD test guidelines 410 and 312, respectively, and were conducted under GLP regulations. The quality of these studies were deemed as "reliable without restrictions."

Genetic Toxicity Mutation - This endpoint is filled with data from a study that followed OECD test guideline 471 and was conducted under GLP regulations. This study utilized *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537. The quality of this study was deemed as "reliable without restrictions".

Aberration - This endpoint is filled with data from an *in vivo* mouse micronucleus test that followed OECD test guideline 473 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions".

Developmental Toxicity - This endpoint is filled by data from a percutaneous exposure study in rats that followed OECD test guideline 414 and was conducted under GLP regulations. The quality of this study was deemed as "reliable with restrictions".

Reproductive Toxicity - This endpoint is filled by data from a dietary exposure study in rats for one-generation that followed OECD test guideline 415 and was conducted under GLP assurances. The quality of this study was deemed as "reliable with restrictions".

Conclusion: **All toxicological endpoints have been satisfied with data from well-conducted studies that followed standardized OECD test guidelines and GLP regulations. The quality of these studies are deemed as**

"reliable without restrictions" and are therefore of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for Primene™ 81-R Amine were obtained from actual testing of this material.

Measured and estimated environmental fate data show that Primene™ 81-R Amine will not persist in the environment. Primene™ 81-R Amine degraded up to 21.8% by day 28 in a closed-bottle test for ready biodegradability. Primary and ultimate biodegradation estimates via QSAR range from days to months, and indicate the chemical will be subject to effective biodegradative processes. Primene™ 81-R Amine is moderately volatile, the measured vapor pressure equaling 0.114 and 0.167 mm Hg at 19 and 24°C, respectively. Primene™ 81-R Amine is soluble in water (1000 mg/l @ 25° C). QSAR estimates of Henry's Law constants show moderate tendency to partition out of the water phase into the atmosphere. Fugacity modeling suggests partitioning largely into soil, with lesser amounts in sediment and aqueous compartments and still less in the atmosphere. The estimated log K_{oc} values approximating 4.0, shows a high degree of adsorption to matrix organic carbon.

The Log P of Primene™ 81-R Amine has been measured at 2.90 and thus significant bioaccumulation in fish will not occur. Accumulation of the chemical within terrestrial species thus is unlikely to occur. The fate and behavior of Primene™ 81-R Amine in wastewater treatment facilities (WWTF) have been estimated. Model results suggest that the up to 89% of the total mass of Primene™ 81-R Amine entering a WWTF would ultimately be removed. Biodegradative losses would be low with the predominant removal mechanism being adsorption to sludge material.

Acute aquatic LC/EC_{50} tests were conducted in rainbow trout (*Oncorhynchus mykiss*), a freshwater invertebrate (*Daphnia magna*) and a freshwater algal species (*Selenastrum capricornutum*). Of these three test organisms, the algae were the most sensitive (72 hour E_rC_{50} = 0.43 mg/L). The 96-hour LC_{50} for trout (1.3 mg/L) and the 48-hour EC_{50} (4.1 mg/L) are qualitatively similar. In a test conducted to estimate the potential chronic toxicity of Primene™ 81-R Amine to the early life-stages of the rainbow trout, the maximum acceptable toxicant concentration (MATC), based on growth was 0.11 mg/L. Therefore, Primene™ 81-R Amine can be classified as toxic (moderate concern) to fish and aquatic invertebrates (appropriate LC/EC_{50} values are greater than 1 mg/L and less than 10 mg/L) and is categorized as very toxic (high concern) to algae (EC_{50} value is less than 1 mg/L).

Primene™ 81-R Amine is considered moderately toxic following acute oral, dermal and inhalation exposures. The oral LD_{50} of rats was 1177 mg/kg for males and 612 mg/kg for females. The oral LD_{50} of mice was 522 mg/kg. The inhalation 4-hr LC_{50} of rats was >231 ppm (> 1.75 mg/L) for males and 157 ppm (1.19 mg/L) in females. The dermal LD_{50} of rats was 251 mg/kg compared to a dermal LD_{50} of 1120 mg/kg in rabbits. Data from skin and eye irritation studies in rabbits indicate that Primene™ 81-R Amine is corrosive to skin and eyes. Primene™

81-R Amine was shown to produce skin sensitization in guinea pigs in a non-adjuvant study (i.e. Buehler) with acetone/ethanol as vehicles. However, use of mineral oil as the vehicle instead of acetone/ethanol, as well as a salt form of Primene™ 81-R Amine in mineral oil, did not produce skin sensitization.

In a 28-day repeated dose study, Primene™ 81-R Amine was administered to rats by dermal application at doses of 0, 5, 20, and 60 mg/kg body weight/day. There were no treatment-related mortalities, clinical signs, or effects on feed consumption. Body weight and cumulative body weight gain were not affected in females of any treatment group. Treatment-related effects on body weight and cumulative body weight gain were observed in high dose males at the end of weeks 1 and 2. Other statistically significant changes in body weight and body weight gain were attributed to solvent exposure. There was no treatment-related effect on any hematologic or clinical chemistry parameters. Increased absolute and relative adrenal weights were observed in both males and females in the high dose group (60 mg/kg/day). Other statistically significant changes in absolute and relative organ weights were attributed to solvent exposure or judged incidental. Local skin irritation was observed at all dose levels, the duration and severity of which were dose-dependent. Treatment-related gross and histopathologic effects were confined to the skin (epidermis and dermis) and underlying subcutaneous tissues at the treatment site. The NOEL for systemic toxicity was 20 mg/kg/day. The minimum effect level was 60 mg/kg/day.

In a four week repeated dose study, the chemical was given to rats via nose-only inhalation for 6 hr per day, 5 days a week for four weeks to vapors of Primene™ 81-R Amine at concentrations of 2, 19, 129, and 537 mg/m^3. No significant clinical signs were observed at 2 or 19 mg/m^3. All animals at 537 mg/m^3 died by exposure day 11. These animals as well as those at the 129 mg/m^3 dose level showed signs of CNS effects (tremors, salivation and lacrimation). After 4 weeks of exposure, none of the survivors showed any effects of CNS effects. Male and female rats exposed to 129 mg/m^3 showed slight focal lesions of the nasal cavity. Microscopic changes at 537 mg/m^3 consisted of effects in the nasal cavity, larynx, trachea, and lung. The NOEL was 19 mg/m^3.

A one-generation reproductive toxicity study of rats was conducted by dietary exposure at 250, 750, and 1500 ppm, approximately equivalent to 20, 59, and 116 mg/kg/day, respectively. Continuous exposure of the chemical in the diet for one generation had a NOEL for parental toxicity of 250 ppm (~20 mg/kg). The reproductive and developmental NOEL was 250 ppm due to decreased pup body weight at both 750 and 1500 ppm and delayed sexual maturation in females at 750 ppm and in both sexes at 1500 ppm. No developmental toxicity was seen in rats treated percutaneously with 5, 15, or 45 mg/kg/day Primene™ 81-R Amine on gestation days 6-20. The developmental NOEL was 45 mg/kg/day and the maternal NOAEL was 5 mg/kg/day. Adverse clinical observations, skin reactions and reductions in body weights and feed consumption were observed in the 15 and/or 45 mg/kg/day dose groups.

Results from mutagenicity and chromosomal aberration studies indicate that Primene™ 81-R Amine is not genotoxic. The chemical was not mutagenic in an Ames mutagenicity assay and did not induce micronuclei in mouse bone marrow in vivo.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on Primene™ 81-R Amine that either followed established protocols under GLP regulations or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to workers and the general population as well as the environment.

EVALUATION OF DATA FOR OUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance and the systematic approach described by Klirnisch *et al*. (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation. The codification described by Klirnisch *et al*. (1997) specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in short abstracts or secondary literature (books, reviews, etc.)

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